

Complete Summary

GUIDELINE TITLE

Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care.

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Mental Health. Bipolar disorder: the management of bipolar disorder in adults, children, and adolescents, in primary and secondary care. Leicester (UK): British Psychological Society, Royal College of Psychiatrists; 2006. 592 p.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Clinical Excellence (NICE). Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. London (UK): National Institute for Clinical Excellence (NICE); 2003 Sep. 26 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- [June 17, 2008 – Antipsychotics \(conventional and atypical\)\]](#): The U.S. Food and Drug Administration (FDA) notified healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. The prescribing information for all antipsychotic drugs will now include information about the increased risk of death in the BOXED WARNING and WARNING sections.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis

RECOMMENDATIONS

EVIDENCE SUPPORTING THE RECOMMENDATIONS

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

CONTRAINDICATIONS

SCOPE

DISEASE/CONDITION(S)

Bipolar disorder

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Pediatrics
Psychiatry
Psychology

INTENDED USERS

Allied Health Personnel
Emergency Medical Technicians/Paramedics
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Occupational Therapists
Pharmacists
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

- To evaluate the role of specific pharmacological agents in the treatment and management of bipolar disorder
- To evaluate the role of specific psychological interventions in the treatment and management of bipolar disorder
- To evaluate the role of specific service delivery systems and service-level interventions in the management of bipolar disorder

- To integrate the above to provide best practice advice on the care of individuals with bipolar disorder through the different phases of illness, including the initiation of treatment, the treatment of acute episodes and the promotion of recovery
- To consider economic aspects of various treatments for bipolar disorder

TARGET POPULATION

Adults and children of all ages who experience bipolar disorder

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Assessment

1. Individual and family history
2. Symptom profile
3. Self-rating scales
4. Family or care giver corroboration
5. Differential diagnosis
6. Risk assessment
7. Age-appropriate diagnostic tools
8. Laboratory tests (e.g., thyroid function tests)

Management

1. Referral to mental health specialist and secondary care services
2. Establishment of collaborative relationships
3. Self-help and support groups
4. Self-monitoring
5. Development of care plans, including advance directives, and crisis plans
6. Consideration of effect of learning disability, comorbid personality disorder, comorbid harmful drug or alcohol use, age
7. Continuity of care
8. Contraception and fetal risk counseling for women of child-bearing potential
9. Frequency of follow-up
10. Management of side-effects (e.g., diabetes, weight gain)
11. Dose regulation (e.g., assessment of blood drug levels)
12. Drug side effect risk management
13. Duration of treatment
14. Life-style and dietary changes
15. Physical monitoring (e.g., smoking, alcohol use, laboratory tests, brain or body scans, drug screening)
16. Inpatient or day patient treatment for children and adolescents
17. Annual review
18. Consideration of special populations, including women who are planning pregnancy or who are pregnant or breastfeeding, and children and adolescents

Treatment

Acute Mania

1. Antipsychotics (olanzapine, quetiapine, risperidone)
2. Lithium
3. Valproate

Acute Depression

1. Antimanic drugs
2. Watchful waiting
3. Selective serotonin reuptake inhibitors (SSRIs)
4. Addition of quetiapine, olanzapine, lithium)
5. Alternative antidepressant (e.g., mirtazapine, venlafaxine)
6. Electroconvulsive therapy (ECT) in individuals with severe depressive illness, catatonia, or a prolonged or severe manic episode
7. Structured psychological interventions

Note: The following were considered but are not recommended: lamotrigine as a single, first-line agent in bipolar I disorder; transcranial magnetic stimulation.

Severe Behavioral Disturbance

1. Oral medication (lorazepam or an antipsychotic or a combination of an antipsychotic and a benzodiazepine)
2. Intramuscular (IM) olanzapine, lorazepam, or haloperidol

Note: The following were considered but are not recommended for routine use for managing behavioral disturbances in people with bipolar disorder: intravenous preparations of any psychotropic drug, IM diazepam, IM chlorpromazine, paraldehyde, and zuclopenthixol.

Long-Term Management

1. Lithium, olanzapine, or valproate
2. Switching or adding agent if patient has frequent relapses
3. Referral to clinician with expertise in bipolar therapy if prophylactic agents are ineffective
4. Lamotrigine or carbamazepine
5. Long-term IM injections of antipsychotics may be considered for patients who were treated successfully for mania with oral antipsychotics but who relapsed because of poor adherence (not recommended for routine use)

Chronic and Recurrent Depressive Symptoms

1. Long-term treatment with SSRIs
2. Cognitive behavioural therapy (CBT) in combination with prophylactic medication
3. Quetiapine
4. Lamotrigine

Long-term Management of Rapid Cycling

1. Combination of lithium and valproate
2. Lithium monotherapy as second-line treatment
3. Combinations of lithium or valproate with lamotrigine

Other Therapies

1. Individual structured psychological intervention
2. Befriending
3. Promoting healthy lifestyle

Note: The guideline does not cover treatments that are not normally available on the National Health Service (NHS).

MAJOR OUTCOMES CONSIDERED

Efficacy Outcomes

- Remission rate
- Symptom levels (mania, depression, psychosis)
- Relapse rate during maintenance therapy (as defined by the study)
- Recurrence rate during acute phase treatment
- Time to recurrence
- Time to clinical outcome (hospitalisation/self-harm)
- Number of adverse clinical outcomes
- Recurrence leading to withdrawal
- Introduction of additional medication
- Number of days participants fulfill criteria for episodes during a time period
- Number of episodes per time period

Acceptability/Tolerability Outcomes

- Rate of discontinuation from treatment for any reason
- Rate of discontinuation from treatment because of side effects
- Number of people reporting side effects
- Number of people leaving a study early because of adverse events
- Number of people reporting specific side effects (weight gain, switching, movement disorders, sedation, cognitive function)
- Symptoms levels for extrapyramidal symptoms (EPS) and akathisia

Other Outcomes

- Medication adherence
- Quality of life/general functioning
- Satisfaction
- Suicide rate
- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Methodology

A step-wise, hierarchical approach was taken to locating and presenting evidence to the Guideline Development Group (GDG). The National Collaborating Centre for Mental Health (NCCMH) developed this process based on methods set out in the *Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers* and after considering recommendations from a range of other sources. These included:

- Centre for Clinical Policy and Practice of the New South Wales Health Department (Australia)
- Clinical Evidence Online
- Cochrane Collaboration
- New Zealand Guidelines Group
- National Health Service (NHS) Centre for Reviews and Dissemination
- Oxford Centre for Evidence-Based Medicine
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Agency for Healthcare Research and Quality
- Oxford Systematic Review Development Programme
- GRADE Working Group

The Review Process

After the scope was finalised, a more extensive search for systematic reviews and published guidelines was undertaken. Existing reviews and relevant guidelines were used for reference to aid the development process.

The GDG decided which questions were likely to have a good evidence base and which questions were likely to have little or no directly relevant evidence. For questions that were unlikely to have a good evidence base, a brief descriptive review was initially undertaken by a member of the GDG (see section 3.5.6 of the full version of the original guideline document). For questions with a good evidence base, the review process depended on the type of clinical question.

Outcomes were also discussed by the GDG and a list drawn up for reference, together with lists of clinical assessment tools and rating scales (Appendix 11 of the full version of the original guideline document).

Searches for evidence were updated every 6 months with the final search 8 weeks before the first consultation. After this last point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

For clinical questions related to interventions, the initial evidence base was formed from well-conducted randomised controlled trials (RCTs) that addressed at least one of the clinical questions (the review process is illustrated in Flowchart 1 of the full version of the original guideline document). Although there are a number of difficulties with the use of RCTs in the evaluation of interventions in mental health, the RCT remains the most important method for establishing treatment

efficacy (this is discussed in more detail in appropriate clinical evidence chapters). For other clinical questions, searches were for the appropriate study design.

Search Strategy

All searches were based on the standard mental health related bibliographic databases (EMBASE, MEDLINE, PsycINFO, CINAHL). At the beginning of the development process, a search for all RCTs relevant to the treatment and management of bipolar disorder was undertaken. Question-specific searches for other clinical questions were undertaken during the development process. In addition, where appropriate, systematic reviews undertaken for other mental health guidelines were updated with newly published trials.

After the initial search results were scanned liberally to exclude obviously irrelevant papers, the review team used a purpose-built 'study information' database to manage all reviewed studies, regardless of whether they met inclusion criteria. For questions relating to interventions without good quality evidence (after the initial search), a decision was made by the GDG about whether to undertake question-specific searches for non-RCT evidence in bipolar disorder or for RCTs in mixed mental health populations, or whether to adopt a consensus process (see Section 3.5.6 of the full version of the original guideline document).

In addition, searches were made of the reference lists of relevant systematic reviews and all included studies, as well as the evidence submitted by stakeholders. Known experts in the field (see Appendix 2 of the full version of the original guideline document), based both on the references identified in early steps and on advice from GDG members, were contacted for trials in the process of being published. In addition, the tables of contents of appropriate journals were checked monthly for relevant studies.

Search Filters

Search filters developed by the review team consisted of a combination of subject heading and free-text phrases. Specific filters were developed for the guideline topic and, where necessary, for each clinical question. In addition, the review team used filters developed for systematic reviews, RCTs and other appropriate research designs (Appendix 6 of the full version of the original guideline document).

Study Selection

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were being entered into the study information database. Appendix 7 of the full version of the original guideline document lists the standard inclusion and exclusion criteria. More specific eligibility criteria were developed for each clinical question and are described in the relevant clinical evidence chapters. Eligible primary-level study papers were critically appraised for methodological quality (see Appendix 7 and Appendix 8 of the full version of the original guideline document). The eligibility of each study was confirmed by at least one member of the appropriate topic group.

For some clinical questions, it was necessary to prioritise the evidence with respect to the United Kingdom (UK) context (that is external validity). To make this process explicit, the GDG took into account the following factors when assessing the evidence:

- Participant factors (for example, age, stage and severity of illness)
- Provider factors (for example, model fidelity, the conditions under which the intervention was performed, the availability of experienced staff to undertake the procedure)
- Cultural factors (for example, differences in standard care, differences in the welfare system)

It was the responsibility of each topic group to decide which prioritisation factors were relevant to each clinical question in light of the UK context and then decide how they should modify their recommendations.

Unpublished Evidence

The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to assess the quality of the data properly. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG did not accept evidence submitted as commercial in confidence. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

Health Economics Review Strategies

A systematic review of the health economic evidence was conducted. Refer to section 3.6 of the full version of the original guideline document for details.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence

The quality of the evidence was based on the quality assessment components (study design, limitations to study quality, consistency, directness and any other modifying factors) and graded using the following definitions:

High - Further research is very unlikely to change confidence in the estimate of the effect.

Moderate - Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate.

Low - Further research is very likely to have an important impact on confidence in the estimate of the effect and is likely to change the estimate.

Very low - Any estimate of effect is very uncertain.

METHODS USED TO ANALYZE THE EVIDENCE

Decision Analysis
Meta-Analysis
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesising the Evidence

Outcome data were extracted from all eligible studies meeting the quality criteria using a standardised form (see Appendix 9 of the full version of the original guideline document). Where possible, meta-analysis was used to synthesise the evidence using Review Manager 4.3.7. If necessary, re-analyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies or reviews.

For a given outcome (continuous and dichotomous), where more than 50% of the number randomised to any group was not accounted for by trial authors, the data were excluded from the review because of the risk of bias. However, where possible, dichotomous efficacy outcomes were calculated on an intention-to-treat basis (that is a 'once-randomised-always-analyse' basis). This assumes that those participants who ceased to engage in the study – from whatever group – had an unfavourable outcome. This meant that the 50% rule was not applied to dichotomous outcomes where there was good evidence that those participants who ceased to engage in the study were likely to have an unfavourable outcome (in this case, early withdrawals were included in both the numerator and denominator). Adverse effects were entered into Review Manager as reported by the study authors because it was usually not possible to determine if early withdrawals had an unfavourable outcome. For the outcome 'leaving the study early for any reason', the denominator was the number randomised.

The number needed to treat – benefit (NNTB) or the number needed to treat – harm (NNTH) was reported for each outcome where the baseline risk (i.e. control group event rate) was similar across studies. In addition, NNTs calculated at follow-up were only reported where the length of follow-up was similar across studies. When the length of follow-up or baseline risk varies (especially with low risk), the NNT is a poor summary of the treatment effect. Risk differences (RD) were calculated for outcomes with low event rates, such as death.

The meta-analysis of survival data, such as time to any mood episode, was based on log hazard ratios and standard errors. Since individual patient data were not available in included studies, hazard ratios and standard errors calculated from a Cox proportional hazard model were extracted. Where necessary, standard errors were calculated from confidence intervals (CIs) or p-value according to standard formulae (for example, Cochrane Reviewers' Handbook 4.2.2). Data were summarised using the generic inverse variance method using Review Manager 4.2.7.

Included/excluded studies tables, generated automatically from the study information database, were used to summarise general information about each study (see Appendix 22 of the full version of the original guideline document). Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were also presented in the study characteristics table (and included, where appropriate, in a narrative review).

Consultation was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing data set. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer was checked by the second reviewer. Disagreements were resolved with discussion. Where consensus could not be reached, a third reviewer resolved the disagreement. Masked assessment (that is blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias.

Summary characteristics tables and, where appropriate, forest plots generated with Review Manager, were presented to the Guideline Development Group (GDP), in order to prepare an evidence profile for each review and to develop recommendations. See the full version of the original guideline document for details of the tables and forest plots.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)
Informal Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Guideline Development Group (GDG) consisted of service users, a carer, and professionals and academic experts in adult, child, and adolescent psychiatry and clinical psychology, nursing, occupational therapy, and general practice. The guideline development process was supported by staff from the National Collaborating Centres for Mental Health (NCCMH), who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline.

Guideline Development Group Meetings

Seventeen GDG meetings were held between March 2004 and March 2006. During each day-long GDG meeting, in a plenary session, clinical and key questions and clinical and economic evidence were reviewed and assessed and recommendations formulated. At each meeting, all GDG members declared any potential conflict of interest, and service user and carer concerns were routinely discussed as part of a standing agenda.

Topic Groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, with GDG members forming smaller topic groups to undertake work in specific areas. Topic group 1 covered questions relating to service delivery; topic group 2 covered pharmacological and other physical treatments; and topic group 3 covered psychological therapies and early warning signs. These groups were designed to manage the large volume of evidence appraisal efficiently before presenting it to the GDG as a whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area. Topic groups refined the key questions, drew up clinical definitions of treatment interventions, reviewed and prepared the evidence with National Collaborating Centre for Mental Health (NCCMH) staff before presenting it to the GDG as a whole and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group's work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG chair in drafting that section of the guideline relevant to the work of each topic group.

Consensus Conferences

Two consensus conferences were held during guideline development. The first addressed the diagnosis of bipolar disorder in children and adolescents; the second, held in collaboration with the GDG developing the NICE guideline for ante- and postnatal mental health, discussed the use of psychotropic medication before, during and after pregnancy. In each, experts from outside the GDG were invited to give presentations and to comment on draft position statements (see chapters 4 and 9, and appendices 19 and 20 of the full version of the original guideline document). Invited experts, additional attendees and external peer reviewers are listed in Appendix 2 of the full version of the original guideline document.

Forming the Clinical Summaries and Recommendations

The evidence profile table relating to a particular clinical question was completed (together with a summary evidence table based on critical outcomes for ease of reference) in Appendix 23 of the full version of the original guideline document. Finally, the systematic reviewer in conjunction with the topic group lead produced a clinical summary.

In order to facilitate consistency in generating and drafting the clinical summaries, a decision tree was used to help determine, for each comparison, the likelihood of the effect being clinically significant (see Figure 3 in the full version of the original guideline document). The decision tree was designed to be used as one step in the interpretation of the evidence (primarily to separate clinically important from

clinically negligible effects) and was not designed to replace clinical judgement. For each comparison, the GDG defined a priori a clinically significant threshold, taking into account both the comparison group and the outcome. Please refer to section 3.5.5. of the full version of the original guideline for further discussion of the decision tree.

Once the evidence profile tables and clinical summaries were finalised and agreed by the GDG, the associated recommendations were produced, taking into account the trade-off between the benefits and risks as well as other important factors. These included economic considerations, values of the GDG and society, and the GDG's awareness of practical issues.

Absence of Appropriately Designed, High-Quality Research

In the absence of level I evidence (or a level that is appropriate to the question), or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there was unlikely to be such evidence, either an informal or formal consensus process was adopted. This process focused on those questions that the GDG considered a priority. Refer to section 3.5.6 of the full version of original guideline document for details about this process.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The following economic issues relating to the epidemiology and the management of bipolar disorder were identified by the Guideline Development Group (GDG) in collaboration with the health economist as primary key issues that should be considered in the guideline:

- The global economic burden of bipolar disorder with specific reference to the United Kingdom (UK)
- Comparative cost-effectiveness between pharmacological, psychological, and physical interventions for the treatment of patients with bipolar disorder either stabilised or experiencing an acute episode
- Comparative cost-effectiveness between different types of service provision appropriate for the management of patients with bipolar disorder

The economic evidence identified by the health economics systematic review was summarised in the respective chapters of the full version of the original guideline document, following presentation of the clinical evidence. The characteristics and results of all economic studies included in the review were provided in the form of evidence tables in Appendix 14 of the full version of the original guideline document. Results of additional economic modelling undertaken alongside the guideline development process are also presented in the relevant chapters.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was validated through two consultations.

1. The first draft of the guideline (The full guideline, National Institute for Clinical Excellence (NICE) guideline and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG)
2. The final consultation draft of the Full guideline, the NICE guideline and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Institute of Health and Clinical Excellence (NICE) and the National Guideline Clearinghouse (NGC): Drug names are marked with an asterisk if they do not have a United Kingdom (UK) marketing authorisation for the indication in question at the time of publication. Prescribers should check each drug's summary of product characteristics (SPC) for current licensed indications.

General Recommendations for the Care of People with Bipolar Disorder

All Patients

Healthcare professionals should establish and maintain collaborative relationships with patients and their families and carers (within the normal bounds of confidentiality), be respectful of the patient's knowledge and experience of the illness, and provide relevant information (including written information) at every stage of assessment, diagnosis, and treatment (including the proper use and likely side-effect profile of medication).

Patients, family and carers should be informed of self-help and support groups and be encouraged to take part in them, particularly at initial diagnosis, and regularly after that. Such groups may provide information on early warning signs, treatment and side effects, and support in time of crisis.

Healthcare professionals should aim to develop a therapeutic relationship with all patients with bipolar disorder, and advise them on careful and regular self-monitoring of symptoms (including triggers and early warning signs), lifestyle (including sleep hygiene and work patterns), and coping strategies.

Advance statements (directives) covering both mental and physical healthcare should be developed collaboratively by people with bipolar disorder and healthcare professionals, especially by people who have severe manic or depressive episodes or who have been treated under the Mental Health Act. These should be documented in care plans, and copies given to the person with bipolar disorder, and to his or her care coordinator and general practitioner (GP).

Healthcare professionals should encourage patients to involve their families and carers in assessment and treatment plans if appropriate, and make themselves accessible to family members and carers in times of crisis. The needs of patients' family members or carers should be taken into account, including:

- The impact of the disorder on relationships
- The welfare of dependent children, siblings, and vulnerable adults
- The regular assessment of carers' physical, social, and mental health needs

Special Groups

People with bipolar disorder who have learning difficulties should receive the same care as others, taking into account the risk of interactions with any other medication they are prescribed.

People with bipolar disorder and comorbid personality disorder should receive the same care as others with bipolar disorder, because the presence of a personality disorder does not preclude the delivery of effective treatments for bipolar disorder.

For people with bipolar disorder and comorbid harmful drug and/or alcohol use, a psychosocial intervention targeted at the drug and/or alcohol use (for example, psychoeducation and motivational enhancement) should be considered. This should normally be delivered by general mental health services, working with specialist substance use services where appropriate.

Local services should have a robust protocol for transferring patients from services for adults of working age to those for older people (usually those older than 65 years). This should include agreement about the clinical parameters to take into account (for example, medical comorbidity or cognitive deterioration) and what to do if the patient is no longer in contact with services for adults of working age. Referral or re-referral should be based on the needs of the patient first, rather than simply their chronological age.

When treating older people with bipolar disorder, healthcare professionals should:

- Be aware of the need to use medication at lower doses
- Be alert to the increased risk of drug interactions when prescribing psychotropic medication to older adults
- Ensure that medical comorbidities have been recognised and addressed

The Assessment, Recognition and Diagnosis of Bipolar Disorder in Adults

Recognising Bipolar Disorder in Primary Care

New or Suspected Presentations of Bipolar Disorder

Primary care clinicians should normally refer patients with suspected bipolar disorder for a specialist mental health assessment and development of a care plan, if either of the following is present:

- Periods of overactive, disinhibited behaviour lasting at least 4 days with or without periods of depression
- Three or more recurrent depressive episodes in the context of a history of overactive, disinhibited behaviour

Primary care clinicians should urgently refer patients with mania or severe depression, and who are a danger to themselves or other people, to specialist mental health services.

Primary care clinicians should ask about hypomanic symptoms when assessing a patient with depression and overactive, disinhibited behaviour.

Existing Bipolar Disorder in Primary Care

When a patient with existing bipolar disorder registers with a practice, the GP should consider referring them for assessment by specialist mental health services and, if appropriate, development of a care plan.

When a patient with bipolar disorder is managed solely in primary care, an urgent referral to secondary care services should be made:

- If there is an acute exacerbation of symptoms, in particular the development of mania or severe depression
- If there is an increase in the degree of risk, or change in the nature of risk, to self or others

When a patient with bipolar disorder is managed solely in primary care, a review by secondary care services or increased contact in primary care should be considered if:

- The patient's functioning declines significantly or their condition responds poorly to treatment.
- Treatment adherence is a problem.
- Comorbid alcohol and/or drug misuse is suspected.
- The patient is considering stopping prophylactic medication after a period of relatively stable mood.

Assessment of Bipolar Disorder in Secondary Care

When assessing suspected bipolar disorder healthcare professionals should:

- Take a full history including family history, a review of all previous episodes, and any symptoms between episodes

- Assess the patient's symptom profile, triggers to previous episodes, social and personal functioning, comorbidities including substance misuse and anxiety, risk, physical health, and current psychosocial stressors
- Obtain where possible, and within the bounds of confidentiality, a corroborative history from a family member or carer
- Consider using formal criteria, including self-rating scales such as the Mood Disorder Questionnaire

When considering a diagnosis of bipolar disorder healthcare professionals should take into account that:

- More pronounced psychotic symptoms, increased suicidal ideation, drug misuse, or more disturbed behaviour may be symptoms of a later presentation of bipolar disorder and not of a schizophrenia-spectrum disorder—this may be particularly important when assessing patients from black and minority ethnic groups who may have difficulty accessing services.
- Drug and/or alcohol misuse may induce manic-like symptoms—in inpatient settings, if there is evidence of misuse, wait 7 days before confirming a diagnosis of bipolar disorder.
- Symptoms may be due to underlying organic conditions, such as hypothyroidism, cerebrovascular insults and other neurological disorders (for example, dementia), particularly in people with late-onset bipolar disorder (older than 40 years).

Before diagnosing rapid-cycling bipolar disorder, healthcare professionals should check alternative explanations for the symptoms including problems such as thyroid disease, antidepressant-induced switching, suboptimal medication regimes, the effects of lithium withdrawal, and erratic compliance. They should also consider asking the patient and/or carer to assess mood and behaviour for at least a year.

When assessing people with suspected bipolar disorder and/or personality disorder healthcare professionals should:

- During initial assessment, consider a diagnosis of bipolar disorder before a diagnosis of personality disorder in a person with mood swings and functional impairment.
- During treatment, ensure the patient has had adequate treatment to stabilise symptoms before considering a diagnosis of comorbid personality disorder.

Assessment of Risk in Primary and Secondary Care

A risk assessment should be undertaken when:

- Bipolar disorder is first diagnosed
- A person with bipolar disorder undergoes significant change in mental state or personal circumstances
- A person with bipolar disorder is discharged from or is on leave from inpatient care

Crisis and Risk Management Plans

If a patient is at risk of suicide, exploitation, or severe self-neglect, is a significant risk to others (including neglect of dependents), or has a history of recurrent admissions, particularly compulsory admissions, a crisis plan should be developed in collaboration with the patient, covering:

- A list of identified or potential personal, social or environmental triggers, and early warning symptoms of relapse
- A protocol for increasing the dose of medication or taking additional medication (which may be given to the patient in advance) for patients who are at risk of rapid onset of mania and for whom clear early warning signs can be identified—protocols should be monitored regularly and are not a substitute for an urgent review
- How primary and secondary healthcare services have agreed to respond to any identified increase in risk, for example by increased contact
- How the patient (and where appropriate their carer) can access help, and the names of healthcare professionals in primary and secondary care who have responsibilities in the crisis plan

A limited quantity of psychotropic medication should be prescribed for patients during periods of high risk of suicide.

Treatment Setting and Pathways to Care

Continuity of Care for People with Bipolar Disorder

People with bipolar disorder (including those with sub-threshold symptoms), whether managed in primary or secondary care, should have continuity of care, and see the same healthcare professionals regularly, where possible, to improve long-term outcomes.

Models of Service Provision

Service Provision in Primary and Secondary Care

Primary and secondary care organisations should consider establishing integrated care programmes for people with bipolar disorder. These should include:

- Regular reviews in primary and secondary care of mental state, and personal and social functioning, to ensure that symptoms (including sub-threshold symptoms) are treated if they significantly impair social functioning
- Clear protocols for the delivery and monitoring of pharmacological, psychosocial, and psychological interventions
- Clear agreements between healthcare professionals on their responsibilities for assessment, monitoring and treatment
- Written treatment plans that promote the principles of self-management, and are shared with the patient and, where appropriate, with families and carers

All GP practices should include people with a diagnosis of bipolar disorder in their case register of people with severe mental illness.

Primary care teams should consider providing telephone support to patients with bipolar disorder, by appropriately trained staff using clear protocols, in particular for monitoring medication regimes.

Specialist Mental Health Services

Referral to a community mental health team should be considered for people with bipolar disorder who:

- Have problems in engaging with and maintaining regular contact with services such as outpatient care
- Experience frequent relapses, poor symptom control, continuing functional impairment, or comorbid anxiety disorders
- Are at risk of suicide, or harm to self or others, including self-neglect or exploitation
- Have problems adhering to medication regimes or with chronic alcohol and/or drug misuse

Crisis resolution and home treatment teams (which should have prompt access to existing care plans) should be considered for people with bipolar disorder to:

- Manage crises at home or in the community
- Support early discharge from hospital

When delivering crisis care at home, particular attention should be given to managing risk, monitoring behavioural disturbance (particularly during episodes of mania), and the burden on family and carers.

Early intervention services for people with psychosis should be available to people with bipolar disorder and should provide specialist expertise in diagnosis and pharmacological, psychological, social, occupational, and educational interventions.

Assertive community treatment should be considered for people with bipolar disorder, particularly those who make high use of inpatient services and those who engage poorly with other services and so experience frequent relapse and/or social breakdown.

Admission to an inpatient unit should be considered for patients with bipolar disorder at significant risk of harm. The unit should provide facilities for containment within a supportive, low-stimulation environment, including access to a psychiatric intensive care unit. The inpatient service should seek to provide an emotionally warm, safe, culturally sensitive and supportive environment, with high levels of positive engagement between staff and patients.

Acute day hospitals should be considered, as an alternative to inpatient care and to facilitate early discharge from inpatient care.

Mental health services, in partnership with social care providers and other local stakeholders should consider providing:

- Vocational rehabilitation – specifically, individual supported placements, for people with bipolar disorder who want help returning to work or gaining employment
- Support to return to or engage with education or other structured, purposeful activities.

Enhanced multiprofessional outpatient clinics, such as lithium clinics, should be considered for patients who would benefit from close monitoring, and/or have a physical health risk such as renal damage, and have a record of regular attendance without the need for outreach services.

Trusts providing specialist mental health services should ensure that all clinicians have access to specialist advice from designated experienced clinicians on managing bipolar disorder in adults (and, where appropriate, separately for children and adolescents), and on referral to tertiary centres.

The Treatment and Management of Bipolar Disorder

General Recommendations

Healthcare professionals should fully involve patients in decisions about their treatment and care, and determine treatment plans in collaboration with the patient, carefully considering the experience and outcome of previous treatment(s) together with patient preference.

Contraception and the risks of pregnancy (including the risks of relapse, damage to the fetus, and the risks associated with stopping or changing medication) should be discussed with all women of child-bearing potential, regardless of whether they are planning a pregnancy. They should be encouraged to discuss pregnancy plans with their doctor.

People experiencing a manic episode, or severe depressive symptoms, should normally be seen again within a week of their first assessment, and then regularly at appropriate intervals, for example, every 2–4 weeks in the first 3 months and less often after that, if response is good.

The Management of Acute Episodes: Mania and Hypomania

General Advice

To help reduce the negative consequences of manic symptoms, healthcare professionals should consider advising patients to avoid excessive stimulation, to engage in calming activities, to delay important decisions, and to establish a structured routine (including a regular sleep pattern) in which the level of activity is reduced.

If a patient is taking an antidepressant at the onset of an acute manic episode, the antidepressant should be stopped. This may be done abruptly or gradually, depending on the patient's current clinical need and previous experience of discontinuation/withdrawal symptoms, and the risk of discontinuation/withdrawal symptoms of the antidepressant in question.

Drug Treatment for Acute Mania for People Not Taking Antimanic Medication

If a patient develops acute mania when not taking antimanic medication, treatment options include starting an antipsychotic, valproate, or lithium. When making the choice, prescribers should take into account preferences for future prophylactic use, the side-effect profile, and consider:

- Prescribing an antipsychotic if there are severe manic symptoms or marked behavioural disturbance as part of the syndrome of mania
- Prescribing valproate or lithium if symptoms have responded to these drugs before, and the person has shown good compliance
- Avoiding valproate in women of child-bearing potential
- Using lithium only if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate

In the initial management of acute behavioural disturbance or agitation, the short-term use of a benzodiazepine (such as lorazepam*) should be considered in addition to the antimanic agent.

If treating acute mania with antipsychotics, olanzapine, quetiapine, or risperidone should normally be used, and the following should be taken into account:

- Individual risk factors for side effects (such as the risk of diabetes)
- The need to initiate treatment at the lower end of the therapeutic dose range recommended in the summary of product characteristics and titrate according to response
- That if an antipsychotic proves ineffective, augmenting it with valproate or lithium should be considered
- That older people are at greater risk of sudden onset of depressive symptoms after recovery from a manic episode

Carbamazepine* should not be routinely used for treating acute mania, and gabapentin*, lamotrigine* and topiramate* are not recommended.

Drug Treatment of Acute Mania for People Taking Antimanic Medication

If a patient already taking an antipsychotic experiences a manic episode, the dose should be checked and increased if necessary. If there are no signs of improvement, the addition of lithium or valproate should be considered.

If a patient already taking lithium experiences a manic episode, plasma lithium levels should be checked. If levels are suboptimal (that is, below 0.8 mmol per litre), the dose should normally be increased to a maximum blood level of 1.0 mmol per litre. If the response is not adequate, augmenting lithium with an antipsychotic should be considered.

If a patient already taking valproate* experiences a manic episode, the dose should be increased until:

- Symptoms start to improve
- Side effects limit further dose increase

If there are no signs of improvement, the addition of olanzapine, quetiapine, or risperidone should be considered. Patients on doses higher than 45 mg per kilogram should be monitored carefully.

For patients who present with severe mania when already taking lithium or valproate*, adding an antipsychotic should be considered at the same time as gradually increasing the dose of lithium or valproate.

For patients who present with mania when already taking carbamazepine, the dose should not routinely be increased. Adding an antipsychotic should be considered, depending on the severity of mania and the current dose of carbamazepine. Interactions with other medication are common with carbamazepine, and doses should be adjusted as necessary.

The Management of Acute Episodes: Depressive Symptoms

Treatment of Depressive Symptoms

Patients Not Taking Antimanic Medication

A patient who is prescribed antidepressant medication should also be prescribed an antimanic drug. The choice of antimanic drug should be compatible with decisions about future prophylactic treatment, the likely side effects and whether the patient is a woman of child-bearing potential.

When initiating antidepressant treatment for a patient who is not already taking antimanic medication, prescribers should explain the risks of switching to mania and the benefits of taking an adjunctive antimanic agent. People who are not willing to take antimanic medication should be monitored carefully. Anti-depressant treatment should begin at a low dose and be increased gradually if necessary.

Patients Taking Antimanic Medication

If a person has an acute depressive episode when taking antimanic medication, prescribers should first check they are taking the antimanic agent at the appropriate dose and adjust the dose if necessary.

Patients with Mild Depressive Symptoms

For patients with acute mild depressive symptoms, a further assessment should be arranged, normally within 2 weeks ('watchful waiting') if:

- Previous episodes of mild depression have not developed into chronic or more severe depression in this patient
- The patient is judged not to be at significant risk of developing a more severe depression

If the patient is judged to be at significant risk of worsening or on review continues to be unwell, they should be managed as for moderate/severe depression particularly if functional impairment is evident.

Patients with Moderate or Severe Depressive Symptoms

For patients with moderate or severe depressive symptoms, prescribers should normally consider:

- Prescribing a selective serotonin reuptake inhibitor (SSRI) antidepressant (but not paroxetine in pregnant women), because these are less likely than tricyclic antidepressants to be associated with switching
- Adding quetiapine, if the patient is already taking antimanic medication that is not an antipsychotic

If a trial of drug treatment at an adequate dose and with adequate compliance does not produce a significant improvement for moderate depressive symptoms, a structured psychological treatment should be considered. This should focus on depressive symptoms, problem solving, promoting social functioning, and education about medication.

Antidepressant Treatment and Risk Monitoring

Antidepressants should be avoided for patients with depressive symptoms who have:

- Rapid-cycling bipolar disorder
- A recent hypomanic episode
- Recent functionally impairing rapid mood fluctuations

Instead, consider increasing the dose of the antimanic agent or the addition of a second antimanic agent (including lamotrigine*).

Patients' concerns about taking antidepressants should be addressed. For example, they should be advised that craving and tolerance do not occur, and that taking medication should not be seen as a sign of weakness.

When antidepressant treatment is started, patients should be told about:

- The possibility of manic or hypomanic switching
- The delay in onset of effect, and the gradual and fluctuating nature of improvement
- The need to take medication as prescribed and the risk of discontinuation/withdrawal symptoms
- The need to monitor for signs of akathisia, suicidal ideation (normally anyone under 30 should be reviewed within 1 week of initiation of treatment), and increased anxiety and agitation (particularly in the initial stages of treatment)
- The need to seek help promptly if these side effects are distressing

If a patient with bipolar disorder develops marked and/or prolonged akathisia or agitation while taking an antidepressant, the use of the drug should be reviewed urgently.

Care should be taken when prescribing SSRIs to people—particularly older people—taking other medication that can cause intestinal bleeding, such as non-

steroidal anti-inflammatory drugs. The use of a gastroprotective drug may be considered.

Stopping Antidepressants after an Acute Depressive Episode

When a patient is in remission from depressive symptoms (or symptoms have been significantly less severe for 8 weeks), stopping the antidepressant medication should be considered, to minimise the risks of switching to mania and increased rapid cycling. The dose of antidepressant should be gradually reduced over several weeks, while maintaining the antimanic medication. Particular care is needed with paroxetine and venlafaxine because they are associated with a higher risk of discontinuation/withdrawal symptoms.

Treatments Not Recommended for Routine Use

The following treatments should not be routinely used for acute depressive episodes in people with bipolar disorder:

- Lamotrigine* as a single, first-line agent in bipolar I disorder
- Transcranial magnetic stimulation*

Treatment Resistance and Psychotic Symptoms

Incomplete Response to the Treatment for Acute Depression

When a patient's depressive symptoms do not fully respond to an antidepressant, the patient should be reassessed for evidence of substance misuse, psychosocial stressors, physical health problems, comorbid disorders, such as anxiety or severe obsessional symptoms, and inadequate adherence to medication. Prescribers should then consider:

- Increasing the dose of the antidepressant within 'British national formulary' ('BNF') limits
- Individual psychological therapy focused on depressive symptoms
- Switching to an alternative antidepressant (for example, mirtazapine or venlafaxine)
- Adding quetiapine* or olanzapine if the patient is not already taking one of these
- Adding lithium if the patient is not already taking it

If a patient's depressive symptoms have failed to respond to at least three courses of treatment for depression of adequate dose and duration, seeking the advice of, or referral to, a clinician with a specialist interest in treating bipolar disorder should be considered.

Concurrent Depressive and Psychotic Symptoms

For patients with a diagnosis of bipolar disorder experiencing concurrent depressive and psychotic symptoms, prescribers should consider augmenting the current treatment plan with antipsychotic medication, such as olanzapine, quetiapine, or risperidone, or the use of electroconvulsive therapy (ECT) (see "The

Use of ECT in Severe Manic and Depressive Episodes" below) if the depressive illness is severe.

Persistent Depressive Symptoms

For patients with persistent depressive symptoms and no history of recent rapid cycling, including those who have declined an antidepressant, structured psychological therapy may be considered. This should focus on depressive symptoms, problem solving, improving social functioning, and further discussion of medication concordance.

Additional Advice

Patients with depressive symptoms should be advised about techniques such as a structured exercise programme, activity scheduling, engaging in both pleasurable and goal-directed activities, ensuring adequate diet and sleep, and seeking appropriate social support, and given increased monitoring and formal support.

The Management of Acute Mixed Episodes

Prescribers should consider treating patients with an acute mixed episode as if they had an acute manic episode, and avoid prescribing an antidepressant.

Prescribers should monitor patients with an acute mixed episode closely (at least weekly), particularly for suicide risk.

The Management of an Acute Episode in Rapid-Cycling Bipolar Disorder

Acute episodes in patients with rapid-cycling bipolar disorder should normally be managed in secondary mental health services. Treatment should be as for manic and depressive episodes, but in addition healthcare professionals should do the following.

- Review the patient's previous treatments for bipolar disorder, and consider a further trial of any that were inadequately delivered or adhered to.
- Focus on optimising long-term treatment rather than on treating individual episodes and symptoms; trials of medication should usually last at least 6 months.
- Adopt a psychoeducational approach and encourage patients to keep a regular mood diary to monitor changes in severity and frequency of symptoms, and the impact of interventions.

The Use of ECT in Severe Manic and Depressive Episodes

Electroconvulsive therapy (ECT) is recommended only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening, in individuals with:

- Severe depressive illness
- Catatonia

- A prolonged or severe manic episode. (Note: This recommendation is from *NICE Technology Appraisal 59*, and has been incorporated into this guideline in line with NICE procedures for the development of guidelines.)

The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including:

- The risks associated with the anaesthetic
- Current comorbidities
- Anticipated adverse events, particularly cognitive impairment
- The risks of not having treatment (Note: This recommendation is from *NICE Technology Appraisal 59*, and has been incorporated into this guideline in line with NICE procedures for the development of guidelines.)

When using ECT to treat bipolar disorder, prescribers should consider:

- Stopping or reducing lithium or benzodiazepines before giving ECT
- Monitoring the length of fits carefully if the patient is taking anticonvulsants.
- Monitoring mental state carefully for evidence of switching to the opposite pole

The Prevention and Management of Behavioural Disturbance

If a patient with bipolar disorder exhibits seriously disturbed behaviour, or is judged to be at risk of doing so, healthcare professionals should:

- Place the patient in the least stimulating and confrontational, and most supportive environment available.
- Review the patient's safety and physical status, including hydration levels, and take appropriate action.
- Consider using distraction techniques and diverting the patient's energy into less risky or more productive activities to prevent or reduce behavioural disturbance.

Drug Treatment of Severe Behavioural Disturbance

The section on the drug treatment of severe behavioural disturbance should be read in conjunction with the NICE clinical guideline on the short-term management of disturbed/violent behaviour in inpatient psychiatric settings and emergency departments (see the National Guideline Clearinghouse [NGC] summary of the NICE guideline, [Violence: the short-term management of disturbed/violent behaviour in psychiatric in-patient settings and emergency departments](#)).

Severe behavioural disturbance in people with bipolar disorder should normally be treated first with oral medication, such as lorazepam* or an antipsychotic, or a combination of an antipsychotic and a benzodiazepine. Risperidone and olanzapine are available in orodispersible formulations that are easier for patients to take and are more difficult to spit out.

If a severely disturbed patient with bipolar disorder cannot be effectively managed with oral medication and rapid tranquilisation is needed, intramuscular olanzapine (10 mg), lorazepam* (2 mg) or haloperidol (2–10 mg) should be considered, wherever possible as a single agent. When making the choice of drug, prescribers should take into account:

- That olanzapine and lorazepam* are preferable to haloperidol because of the risk of movement disorders (particularly dystonia and akathisia) with haloperidol
- That olanzapine and benzodiazepines should not be given intramuscularly within 1 hour of each other
- That repeat intramuscular doses can be given up to 20 mg per day (olanzapine), or 4 mg per day (lorazepam*) or 18 mg per day (haloperidol)—the total daily dose including concurrent oral medication should not normally exceed 'BNF' limits
- The patient's previous response and tolerability, their current regular medication, and the availability of flumazenil

Intravenous preparations of any psychotropic drug, intramuscular diazepam*, intramuscular chlorpromazine, paraldehyde* and zuclopenthixol acetate are not recommended for routine use for managing behavioural disturbances in people with bipolar disorder.

The Long-Term Management of Bipolar Disorder

Drug Treatment after Recovery from an Acute Episode

Prescribers should consider starting long-term treatment for bipolar disorder:

- After a manic episode that was associated with significant risk and adverse consequences
- When a patient with bipolar I disorder has had two or more acute episodes
- When a patient with bipolar II disorder has significant functional impairment, is at significant risk of suicide, or has frequent episodes

Lithium, olanzapine or valproate* should be considered for long-term treatment of bipolar disorder. The choice should depend on:

- Response to previous treatments
- The relative risk, and known precipitants, of manic versus depressive relapse
- Physical risk factors, particularly renal disease, obesity, and diabetes
- The patient's preference and history of adherence
- Gender (valproate* should not be prescribed for women of childbearing potential)
- A brief assessment of cognitive state (such as the Mini-Mental State Examination) if appropriate, for example, for older people

If the patient has frequent relapses, or symptoms continue to cause functional impairment, switching to an alternative monotherapy or adding a second prophylactic agent (lithium, olanzapine, valproate*) should be considered. Clinical state, side effects and, where relevant, blood levels should be monitored closely.

Possible combinations are lithium with valproate*, lithium with olanzapine*, and valproate with olanzapine*. The reasons for the choice and the discussion with the patient of the potential benefits and risks should be documented.

If a trial of a combination of prophylactic agents proves ineffective, the following should be considered:

- Consulting with, or referring the patient to, a clinician with expertise in the drug treatment of bipolar disorder
- Prescribing lamotrigine* (especially if the patient has bipolar II disorder) or carbamazepine

Long-term drug treatment should normally continue for at least 2 years after an episode of bipolar disorder, and up to 5 years if the person has risk factors for relapse, such as a history of frequent relapses or severe psychotic episodes, comorbid substance misuse, ongoing stressful life events, or poor social support. This should be discussed with the patient and there should be regular reviews. Patients who wish to stop medication early should be encouraged to discuss this with their psychiatrist.

If, after careful discussion, a patient with bipolar disorder declines long-term medication, they should still be offered regular contact and reassessment with primary or secondary care services.

Long-acting intramuscular injections of antipsychotics ('depots') are not recommended for routine use in bipolar disorder. They may be considered for people who were treated successfully for mania with oral antipsychotics, but have had a relapse because of poor adherence.

After an Acute Depressive Episode

After successful treatment for an acute depressive episode, patients should not normally continue on antidepressant treatment long-term because there is no evidence that this reduces relapse rates, and it may be associated with increased risk of switching to mania.

Treatment for Chronic and Recurrent Depressive Symptoms

The following treatments should be considered, in discussion with the patient, for people who have an established diagnosis of bipolar disorder and chronic or recurrent depressive symptoms, but who are not taking prophylactic medication and have not had a recent manic/hypomanic episode:

- Long-term treatment with SSRIs at the minimum therapeutic dose in combination with prophylactic medication
- Cognitive behavioural therapy (16–20 sessions) in combination with prophylactic medication
- Quetiapine*
- Lamotrigine*

For patients with bipolar II disorder with recurrent depression, lamotrigine* alone should be considered for long-term treatment.

Long-Term Management of Rapid Cycling

For the long-term management of rapid-cycling bipolar disorder prescribers should:

- Consider as first-line treatment a combination of lithium and valproate*.
- Consider lithium monotherapy as second-line treatment; for patients already taking lithium consider increasing the dose.
- Avoid the use of an antidepressant, except on advice from a specialist in bipolar disorder.
- Consider combinations of lithium or valproate* with lamotrigine*, especially in bipolar II disorder.
- Check thyroid function every 6 months together with levels of thyroid antibodies if clinically indicated, for example, by the thyroid function tests.

Comorbid Anxiety Disorders

For patients with significant comorbid anxiety disorders, psychological treatment focused on anxiety or treatment with a drug such as an atypical antipsychotic should be considered.

Promoting a Healthy Lifestyle and Relapse Prevention

Patients with bipolar disorder should be given advice (including written information) on:

- The importance of good sleep hygiene and a regular lifestyle
- The risks of shift work, night flying and flying across time zones, and routinely working excessively long hours, particularly for patients with a history of relapse related to poor sleep hygiene or irregular lifestyle
- Ways to monitor their own physical and mental state

People with bipolar disorder should be given additional support after significant life events, such as loss of job or a close bereavement. This should include increased monitoring of mood and general well-being, and encouraging the patient to discuss difficulties with family and friends.

Healthcare professionals, in collaboration with patients, should develop a plan to identify the symptoms and indicators of a potential exacerbation of the disorder, and how to respond (including both psychosocial and pharmacological interventions).

Psychological Therapy after Recovery from an Acute Episode

Individual structured psychological interventions should be considered for people with bipolar disorder who are relatively stable, but may be experiencing mild to moderate affective symptoms. The therapy should be in addition to prophylactic

medication, should normally be at least 16 sessions (over 6–9 months) and should:

- Include psychoeducation about the illness, and the importance of regular daily routine and sleep and concordance with medication
- Include monitoring mood, detection of early warnings and strategies to prevent progression into full-blown episodes
- Enhance general coping strategies

Structured psychological interventions should be delivered by people who are competent to do this and have experience of patients with bipolar disorder.

Healthcare professionals should consider offering a focused family intervention to people with bipolar disorder in regular contact with their families, if a focus for the intervention can be agreed. The intervention should take place over 6–9 months, and cover psychoeducation about the illness, ways to improve communication, and problem solving.

Psychosocial Support

Healthcare professionals should consider offering befriending to people who would benefit from additional social support, particularly those with chronic depressive symptoms. Befriending should be in addition to drug and psychological treatments, and should be by trained volunteers providing, typically, at least weekly contact for between 2 and 6 months.

The Physical Care of People with Bipolar Disorder

See Appendix 21 of the full version of the original guideline document for a list of physical monitoring tests.

Initial Physical Assessment

As soon as practicable after initial presentation of a patient with bipolar disorder, healthcare professionals should:

- Establish the patient's smoking status and alcohol use
- Perform thyroid, liver, and renal function tests, blood pressure, and measure full blood count, blood glucose, lipid profile
- Measure weight and height
- Consider electroencephalography (EEG), computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan if an organic aetiology or a relevant comorbidity is suspected
- Consider drug screening, chest x-ray and electrocardiogram (ECG) if suggested by the history or clinical picture

Initiating, Monitoring and Stopping Drug Treatments

The Long-Term Use of Antipsychotics

Initiating Antipsychotics

When initiating long-term treatment of bipolar disorder with antipsychotics, weight and height, plasma glucose, and lipids should be measured in all patients, and an ECG arranged for patients with risk factors for cardiovascular disease or risk factors for it. Prolactin levels should be measured when initiating risperidone* in patients with low libido, sexual dysfunction, menstrual abnormalities, gynaecomastia, or galactorrhea.

When initiating quetiapine*, the dose should be titrated gradually (in line with the summary of product characteristics), to help maintain normal blood pressure.

Monitoring Antipsychotics

Patients taking antipsychotics should have their weight checked every 3 months for the first year, and more often if they gain weight rapidly. Plasma glucose and lipids (preferably fasting levels) should be measured 3 months after the start of treatment (and within 1 month if taking olanzapine), and more often if there is evidence of elevated levels. In patients taking risperidone*, prolactin levels should be measured if symptoms of raised prolactin develop; these include low libido, sexual dysfunction, menstrual abnormalities, gynaecomastia, and galactorrhea.

Stopping Antipsychotics

If a patient with bipolar disorder is stopping antipsychotic medication, the antipsychotic:

- Should be stopped gradually over at least 4 weeks if the patient is continuing with other medication
- Should be stopped over a period of up to 3 months if the patient is not continuing with other medication, or has a history of manic relapse

Risks Associated with the Use of Antipsychotics

Healthcare professionals should discuss with patients the risk of weight gain, and be aware of the possibility of worsening existing diabetes, malignant neuroleptic syndrome, and diabetic ketoacidosis with the use of antipsychotic medication; particular caution is needed when treating patients with mania.

The Long-Term Use of Lithium

Initiating Lithium

Lithium should not be initiated routinely in primary care for the treatment of bipolar disorder.

When initiating lithium as long-term treatment, prescribers should:

- Advise patients that erratic compliance or rapid discontinuation may increase the risk of manic relapse
- Measure height and weight, and arrange tests for urea and electrolytes and serum creatinine, and thyroid function
- Arrange an ECG for patients with cardiovascular disease or risk factors for it

- Arrange a full blood count if clinically indicated
- Establish a shared-care protocol with the patient's GP for prescribing and monitoring lithium and checking for adverse effects
- Be aware that patients should take lithium for at least 6 months to establish its effectiveness as a long-term treatment

Serum lithium levels should be checked 1 week after starting and 1 week after every dose change, and until the levels are stable. The aim should be to maintain serum lithium levels between 0.6 and 0.8 mmol per litre in people being prescribed it for the first time.

For people who have relapsed previously while taking lithium or who still have sub-threshold symptoms with functional impairment while receiving lithium, a trial of at least 6 months with serum lithium levels between 0.8 and 1.0 mmol per litre should be considered.

Monitoring Lithium

For patients with bipolar disorder on lithium treatment, prescribers should do the following.

- Monitor serum lithium levels normally every 3 months.
- Monitor older adults carefully for symptoms of lithium toxicity, because they may develop high serum levels of lithium at doses in the normal range, and lithium toxicity is possible at moderate serum lithium levels.
- Monitor weight, especially in patients with rapid weight gain.
- Undertake more frequent tests if there is evidence of clinical deterioration, abnormal results, a change in sodium intake, or symptoms suggesting abnormal renal or thyroid function such as unexplained fatigue, or other risk factors, for example, if the patient is starting medication such as angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs, or diuretics.
- Arrange thyroid and renal function tests every 6 months, and more often if there is evidence of impaired renal function.
- Initiate closer monitoring of lithium dose and blood serum levels if urea and creatinine levels become elevated, and assess the rate of deterioration of renal function. The decision whether to continue lithium depends on clinical efficacy, and degree of renal impairment; prescribers should consider seeking advice from a renal specialist and a clinician with expertise in the management of bipolar disorder on this.
- Monitor for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic levels.

Stopping Lithium

Lithium should be stopped gradually over at least 4 weeks, and preferably over a period of up to 3 months, particularly if the patient has a history of manic relapse (even if they have been started on another antimanic agent).

When lithium treatment is stopped or is about to be stopped abruptly, prescribers should consider changing to monotherapy with an atypical antipsychotic or valproate*, and then monitor closely for early signs of mania and depression.

Risks Associated with the Use of Lithium

Patients taking lithium should be warned not to take over-the-counter non-steroidal anti-inflammatory drugs. Prescribing non-steroidal antiinflammatory drugs for such patients should be avoided if possible, and if they are prescribed the patient should be closely monitored.

Patients taking lithium should be advised to:

- Seek medical attention if they develop diarrhoea and/or vomiting
- Ensure they maintain their fluid intake, particularly after sweating (for example, after exercise, in hot climates, or if they have a fever), if they are immobile for long periods or—in the case of older people—develop a chest infection or pneumonia
- Consider stopping lithium for up to 7 days if they become acutely and severely ill with a metabolic or respiratory disturbance from whatever cause

The Long-Term Use of Valproate

Initiating Valproate

Valproate should not be routinely initiated in primary care for the treatment of bipolar disorder.

When initiating valproate* as long-term treatment, patients should have their height and weight measured, and have a full blood count and liver function tests.

Valproate* should not be prescribed routinely for women of child-bearing potential. If no effective alternative to valproate can be identified, adequate contraception should be used, and the risks of taking valproate during pregnancy should be explained.

Valproate* should not be prescribed for young women with bipolar disorder who are younger than 18 years because of the risk of polycystic ovary syndrome and unplanned pregnancy in this age group.

Monitoring Valproate*

Routine measurement of valproate* blood levels is not recommended unless there is evidence of ineffectiveness, poor adherence, or toxicity.

Liver function tests and a full blood count should be done after 6 months' treatment with valproate*, and weight should be monitored in patients who gain weight rapidly.

Stopping Valproate*

When stopping valproate* in patients with bipolar disorder, the dose should be reduced gradually over at least 4 weeks to minimise the risk of destabilisation.

Risks Associated with the Use of Valproate*

Patients on valproate*, and their carers, should be advised how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if these develop. If abnormal liver function or blood dyscrasia is detected the drug should be stopped immediately.

When prescribing valproate*, prescribers should be aware of:

- Its interactions with other anticonvulsants
- The need for more careful monitoring of sedation, tremor and gait disturbance in older people

Lamotrigine

Initiating Lamotrigine

Lamotrigine should not be routinely initiated in primary care for the treatment of bipolar disorder.

The dose of lamotrigine* should be titrated gradually to minimise the risk of skin rashes, including Stevens–Johnson syndrome. Titration should be slower in patients also taking valproate.

When offering lamotrigine* to women taking oral contraceptives, prescribers should explain that the drug may decrease the effectiveness of the contraceptive and discuss alternative methods of contraception. If a woman taking lamotrigine* stops taking an oral contraceptive, the dose of lamotrigine* may need to be reduced by up to 50%.

Monitoring Lamotrigine

Routine monitoring of blood levels of lamotrigine* is not needed.

Stopping Lamotrigine

When stopping lamotrigine*, the dose should be reduced gradually over at least 4 weeks to minimise the risk of destabilisation.

Risks Associated with the Use of Lamotrigine

Patients taking lamotrigine* should be advised, particularly when starting the drug, to seek medical attention urgently if a rash develops. The drug should be stopped unless it is clear that the rash is not related to the use of lamotrigine*. If an appointment cannot be arranged within a few days or if the rash is worsening, the patient should be advised to stop the drug and then restart if lamotrigine* is not implicated in the development of the rash.

Carbamazepine

Initiating Carbamazepine

Carbamazepine should be used for the long-term treatment of bipolar disorder only after consulting a specialist.

The dose of carbamazepine should be increased gradually to reduce the risk of ataxia.

When initiating carbamazepine as long-term treatment, patients should have their height and weight measured, and have a full blood count and liver function tests.

Monitoring Carbamazepine

Plasma levels of carbamazepine should be measured every 6 months to exclude toxicity, because therapeutic levels and toxic levels are close.

Liver function tests and a full blood count should be repeated after 6 months' treatment with carbamazepine, and weight should be monitored in patients who gain weight rapidly.

Blood urea and electrolytes should be measured every 6 months after starting treatment with carbamazepine to check for hyponatraemia.

Possible interactions of carbamazepine with other drugs, including oral contraceptives, should be monitored closely, particularly if the patient starts a new medication.

Stopping Carbamazepine

The dose of carbamazepine should be reduced gradually over at least 4 weeks to minimise the risk of destabilisation.

Risks Associated with the Use of Carbamazepine

When prescribing carbamazepine for patients taking concomitant medications—for example, people older than 65 years and people with multiple physical problems—prescribers should be aware that carbamazepine has a greater potential for drug interactions than other drugs used to treat bipolar disorder.

Annual Review of Physical Health

People with bipolar disorder should have an annual physical health review, normally in primary care, to ensure that the following are assessed each year:

- Lipid levels, including cholesterol in all patients over 40 even if there is no other indication of risk
- Plasma glucose levels
- Weight
- Smoking status and alcohol use
- Blood pressure

The results of the annual review should be given to the person, and to healthcare professionals in primary and secondary care (including whether the person

refused any tests). A clear agreement should be made about responsibility for treating any problems.

Weight Gain Management

If a person gains weight during treatment their medication should be reviewed, and the following considered:

- Dietary advice and support from primary care and mental health services
- Advising regular aerobic exercise
- Referral to mental health services for specific programmes to manage weight gain
- Referral to a dietician if the person has complex comorbidities (for example, coeliac disease)

Drug treatments such as high-dose antidepressants, sibutramine, or topiramate* are not recommended to promote weight loss.

Women with Bipolar Disorder Who Are Planning a Pregnancy, Pregnant or Breastfeeding

General Principles of Management for Women

The absolute and relative risks of problems associated with both treating and not treating the bipolar disorder during pregnancy should be discussed with women.

More frequent contact by specialist mental health services (including, where appropriate, specialist perinatal mental health services), working closely with maternity services, should be considered for pregnant women with bipolar disorder, because of the increased risk of relapse during pregnancy and the postnatal period.

A written plan for managing a woman's bipolar disorder during the pregnancy, delivery, and postnatal period should be developed as soon as possible. This should be developed with the patient and significant others, and shared with her obstetrician, midwife, GP and health visitor. All medical decisions should be recorded in all versions of the patient's notes. Information about her medication should be included in the birth plan and notes for postnatal care.

If a pregnant woman with bipolar disorder is stable on an antipsychotic and likely to relapse without medication, she should be maintained on the antipsychotic, and monitored for weight gain and diabetes.

The following drugs should not be routinely prescribed for pregnant women with bipolar disorder:

- Valproate—because of risk to the fetus and subsequent child development
- Carbamazepine—because of its limited efficacy and risk of harm to the fetus
- Lithium—because risk of harm to the fetus, such as cardiac problems
- Lamotrigine*—because of the risk of harm to the fetus
- Paroxetine—because of the risk of cardiovascular malformations in the fetus

- Long-term treatment with benzodiazepines—because of risks during pregnancy and the immediate postnatal period, such as cleft palate and floppy baby syndrome.

Women Planning a Pregnancy

Women with bipolar disorder who are considering pregnancy should normally be advised to stop taking valproate, carbamazepine, lithium, and lamotrigine*, and alternative prophylactic drugs (such as an antipsychotic) should be considered.

Women taking antipsychotics who are planning a pregnancy should be advised that the raised prolactin levels associated with some antipsychotics reduce the chances of conception. If prolactin levels are raised, an alternative drug should be considered.

If a woman who needs antimanic medication plans to become pregnant, a low-dose typical or atypical antipsychotic should be considered, because they are of least known risk.

If a woman taking lithium plans to become pregnant, the following options should be considered:

- If the patient is well and not at high risk of relapse—gradually stopping lithium
- If the patient is not well or is at high risk of relapse:
 - Switching gradually to an antipsychotic
 - Stopping lithium and restarting it in the second trimester if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past
 - Continuing with lithium, after full discussion of the risks, while trying to conceive and throughout the pregnancy, if manic episodes have complicated the woman's previous pregnancies, and her symptoms have responded well to lithium.

If a woman remains on lithium during pregnancy, serum lithium levels should be monitored every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth. The dose should be adjusted to keep serum levels within the therapeutic range. The woman should maintain adequate fluid intake.

If a woman planning a pregnancy becomes depressed after stopping prophylactic medication, psychological therapy (cognitive behavioral therapy [CBT]) should be offered in preference to an antidepressant because of the risk of switching associated with antidepressants. If an antidepressant is used, it should usually be an SSRI (but not paroxetine because of the risk of cardiovascular malformations in the fetus) and the woman should be monitored closely.

Women with an Unplanned Pregnancy

If a woman with bipolar disorder has an unplanned pregnancy:

- The pregnancy should be confirmed as quickly as possible.

- The woman should be advised to stop taking valproate, carbamazepine, and lamotrigine*.
- If the pregnancy is confirmed in the first trimester, and the woman is stable, lithium should be stopped gradually over 4 weeks, and the woman informed that this may not remove the risk of cardiac defects in the fetus.
- If the woman remains on lithium during pregnancy serum lithium levels should be checked every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth; the dose should be adjusted to keep serum levels within the therapeutic range, and the woman should maintain adequate fluid intake.
- An antipsychotic should be offered as prophylactic medication.
- Offer appropriate screening and counselling about the continuation of the pregnancy, the need for additional monitoring and the risks to the fetus if the woman stays on medication.

If a woman with bipolar disorder continues with an unplanned pregnancy, the newborn baby should have a full paediatric assessment, and social and medical help should be provided for the mother and child.

Pregnant Women with Acute Mania or Depression

Acute Mania

If a pregnant woman who is not taking medication develops acute mania, an atypical or a typical antipsychotic should be considered. The dose should be kept as low as possible and the woman monitored carefully.

If a pregnant woman develops acute mania while taking prophylactic medication, prescribers should:

- Check the dose of the prophylactic agent and adherence
- Increase the dose if the woman is taking an antipsychotic, or consider changing to an antipsychotic if she is not
- If there is no response to changes in dose or drug and the patient has severe mania, consider the use of ECT, lithium and, rarely, valproate

If there is no alternative to valproate the woman should be informed of the increased risk to the fetus and the child's intellectual development. The lowest possible effective dose should be used and augmenting it with additional antimanic medication (but not carbamazepine*) considered. The maximum dosage should be 1 gram per day, in divided doses and in the slow-release form, with 5 mg/day folic acid.

Depressive Symptoms

For mild depressive symptoms in pregnant women with bipolar disorder the following should be considered:

- Self-help approaches such as guided self-help and computerised CBT
- Brief psychological interventions
- Antidepressant medication

For moderate to severe depressive symptoms in pregnant women with bipolar disorder the following should be considered:

- Psychological treatment (CBT) for moderate depression
- Combined medication and structured psychological interventions for severe depression

For moderate to severe depressive symptoms in pregnant women with bipolar disorder, quetiapine* alone or SSRIs (but not paroxetine) in combination with prophylactic medication should be preferred because SSRIs are less likely to be associated with switching than the tricyclic antidepressants. Monitor closely for signs of switching and stop the SSRI if patients start to develop manic or hypomanic symptoms.

Women who are prescribed an antidepressant during pregnancy should be informed of the potential, but predominantly short-lived, adverse effects of antidepressants on the neonate.

Care in the Perinatal Period

Women taking lithium should deliver in hospital, and be monitored during labour by the obstetric medical team, in addition to usual midwife care. Monitoring should include fluid balance, because of the risk of dehydration and lithium toxicity.

After delivery, if a woman with bipolar disorder who is not on medication is at high risk of developing an acute episode, prescribers should consider establishing or reinstating medication as soon as the patient is medically stable (once the fluid balance is established).

If a woman maintained on lithium is at high risk of a manic relapse in the immediate postnatal period, augmenting treatment with an antipsychotic should be considered.

If a woman with bipolar disorder develops severe manic or psychotic symptoms and behavioural disturbance in the intrapartum period rapid tranquillisation with an antipsychotic should be considered in preference to a benzodiazepine because of the risk of floppy baby syndrome. Treatment should be in collaboration with an anaesthetist.

Breastfeeding

Women with bipolar disorder who are taking psychotropic medication and wish to breastfeed should:

- Have advice on the risks and benefits of breastfeeding
- Be advised not to breastfeed if taking lithium, benzodiazepines, or lamotrigine*, and offered a prophylactic agent that can be used when breastfeeding—an antipsychotic should be the first choice (but not clozapine*)
- Be prescribed an SSRI if an antidepressant is used (but not fluoxetine or citalopram)

Care of the Infant

- Babies whose mothers took psychotropic drugs during pregnancy should be monitored in the first few weeks for adverse drug effects, drug toxicity, or withdrawal (for example, floppy baby syndrome, irritability, constant crying, shivering, tremor, restlessness, increased tone, feeding and sleeping difficulties, and rarely seizures). If the mother was prescribed antidepressants in the last trimester, such symptoms may be a serotonergic toxicity syndrome rather than withdrawal, and the neonate should be monitored carefully.

Children and Adolescents with Bipolar Disorder

Special Considerations

Healthcare professionals working in specialist services with children and adolescents with bipolar disorder should:

- Be familiar with local and national guidelines on confidentiality and the rights of the child
- Ensure appropriate consent is obtained, considering the adolescent's understanding (including Gillick competence), parental consent and responsibilities, child protection matters, and the use of the Mental Health Act and of the Children Act (1989)

When planning the care of children and adolescents with bipolar disorder, healthcare professionals should consider:

- Stressors and vulnerabilities in their social, educational, and family environments, including the quality of interpersonal relationships
- The impact of any comorbidities, such as attention deficit hyperactivity disorder (ADHD) and anxiety disorders
- The impact of the disorder on their social inclusion and education
- Their vulnerability to exploitation, for example, as a result of disinhibited behaviour

Parents or carers (and possibly other family members) should be involved in developing care plans so that they can give informed consent, support the psychological goals of treatment, and help to ensure treatment adherence.

Children and adolescents should be offered separate individual appointments with a healthcare professional in addition to joint meetings with their family members or carers.

Diagnosing Bipolar I Disorder in Prepubescent Children

When diagnosing bipolar I disorder in prepubescent children the same criteria should be used as in adults except that:

- Mania must be present
- Euphoria must be present most days, most of the time (for a period of 7 days)

- Irritability is not a core diagnostic criterion

Bipolar I disorder should not be diagnosed solely on the basis of a major depressive episode in a child with a family history of bipolar disorder. However, children with a history of depression and a family history of bipolar disorder should be carefully followed up.

Diagnosing Bipolar I Disorder in Adolescents

When diagnosing bipolar I disorder in adolescents the same criteria should be used as for adults except that:

- Mania must be present
- Euphoria must be present most days, most of the time (for at least 7 days)
- Irritability can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character; however, it should not be a core diagnostic criterion

Bipolar I disorder should not be diagnosed solely on the basis of a major depressive episode in an adolescent with a family history of bipolar disorder. However, adolescents with a history of depression and a family history of bipolar disorder should be carefully followed up.

Diagnosing Bipolar I Disorder in Older or Developmentally Advanced Adolescents

In older or developmentally advanced adolescents, the criteria for establishing a diagnosis of bipolar I disorder in adults should be used.

Bipolar II Disorder in Both Children and Adolescents

Bipolar II disorder should not normally be diagnosed in children or adolescents because the diagnostic criteria are not well-enough established for routine use.

In older or developmentally advanced adolescents, the criteria for diagnosing bipolar II disorder in adults should be used.

Differential Diagnosis for Children and Adolescents

The presence of clear-cut episodes of unduly elated mood, inappropriate and impairing grandiosity, and cycles of mood should be used to distinguish bipolar I disorder from attention deficit hyperactivity disorder (ADHD) and conduct disorder.

The presence of mood cycles should be used to distinguish bipolar disorder from schizophrenia.

Before diagnosing bipolar I disorder in a child or adolescent, other possible explanations for the behaviour and symptoms should be considered, including:

- Sexual, emotional, and physical abuse if they show disinhibition, hypervigilance, or hypersexuality
- The possibility of drug and/or alcohol misuse as a cause of mania-like symptoms; consider a diagnosis of bipolar disorder only after 7 days of abstinence
- Previously undiagnosed learning difficulties
- Organic causes such as excited confusional states in children with epilepsy, and akathisia resulting from neuroleptic medication

Children and Adolescents with Learning Difficulties

When diagnosing bipolar I disorder in a child or adolescent with learning difficulties, the same criteria as are applied to children and adolescents without learning difficulties should be used.

Children and Adolescents with Sub-Threshold Symptoms of Bipolar Disorder

If it is not possible to make a diagnosis in a child or adolescent with sub-threshold symptoms of bipolar disorder, they should be carefully followed up.

Assessment Methods for Children and Adolescents

The diagnosis of bipolar disorder in children and adolescents should be made by a clinician with specialist training in child and adolescent mental health.

Assessment should include:

- A detailed mental state examination based on an individual interview with the child
- A medical evaluation to exclude organic causes
- Further neuropsychological and neurological evaluation as appropriate
- A detailed account of the presenting problem from the child, parents or carers, and other significant adults such as teachers
- A detailed developmental and neurodevelopmental history, including birth history, speech and language development, behaviour problems, attachment behavior, and any history of abuse

A specialist diagnostic instrument such as the WASH-U-KSADS may be used; scales completed by parents or carers such as the Child Behaviour Checklist, Conners' Abbreviated Rating Scale, Parent Young Mania Rating Scale and Parent General Behaviour Inventory may also be used. These should not replace a full clinical interview.

In severely mentally ill children and adolescents with psychotic symptoms, a diagnosis should be attempted as early as practical, and should be subject to regular specialist review.

Drug Treatment of Acute Mania in Children and Adolescents

When prescribing medication for children or adolescents with an acute manic episode, the recommendations for adults with bipolar disorder should be followed except drugs should be initiated at lower doses. In addition, at initial presentation:

- Height and weight should be checked (and monitored regularly afterwards—for example, monthly for 6 months then every 6 months).
- Prolactin levels should be measured.
- When considering an antipsychotic, the risk of increased prolactin levels with risperidone* and weight gain with olanzapine* should be considered.
- Where there is an inadequate response to an antipsychotic, adding lithium or valproate* should be considered. Valproate should normally be avoided in girls and young women because of risks during pregnancy and because of the risk of polycystic ovary syndrome.

Drug And Psychological Treatments of Depression in Children and Adolescents

Children and adolescents with bipolar disorder experiencing mild depressive symptoms assessed as not requiring immediate treatment should be monitored weekly and offered additional support, for example at home and in school.

Children or adolescents with depressive symptoms needing treatment should normally be treated by specialist clinicians (based in at least Tier 3 services, specialised child and adolescent mental health services for severe, complex, or persistent disorders. Staff include child and adolescent psychiatrists, clinical psychologists, nurses, and child and adolescent psychotherapists). Treatment should be as for adults with bipolar disorder except that a structured psychological therapy aimed at treating depression should be considered in addition to prophylactic medication.

If there has been no response to psychological therapy for depression combined with prophylactic medication after 4 weeks, prescribers should consider:

- Adding fluoxetine* starting at 10 mg per day, and increasing to 20 mg per day if needed
- Using an alternative SSRI (sertraline* or citalopram*) if there is no response to fluoxetine after an adequate trial.

If there is still no response advice should be sought from a specialist in affective disorders.

For developmentally advanced adolescents with depressive symptoms, the recommendations on managing depression in adults with bipolar disorder should be followed.

Long-Term Treatment of Children and Adolescents

Long-term management of children or adolescents with bipolar disorder should normally be by specialist clinicians (based in at least Tier 3 services). Treatment should be as for adults with bipolar disorder except that:

- An atypical antipsychotic that is associated with lower weight gain and non-elevation of prolactin levels should be the first-line prophylactic agent.
- Lithium should be considered as the second-line prophylactic agent in female patients and valproate or lithium as the second-line prophylactic agent in male patients.
- Parents and carers should be given support to help the patient maintain a regular lifestyle.
- The school or college should be given advice (with permission of the patient and those with parental responsibility) on managing the patient's bipolar disorder.

Inpatient Services for Children and Adolescents

Admission as an inpatient or day patient, or more intensive community treatment, should be considered for children and adolescents at risk of suicide or other serious harm. Such care should be provided in specialist units, designed specifically for children and adolescents and able to support their educational, social and personal needs.

Severe behavioural disturbance in children and adolescents with bipolar disorder should be managed as for adults, except that rapid tranquillisation with haloperidol* is not recommended because of the increased risk of extrapyramidal side effects in this age group.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation is discussed and presented in evidence tables in the relevant section of the full version of the original guideline document.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis, treatment, and management of acute and chronic episodes of bipolar I or II disorder

POTENTIAL HARMS

Side effects of medication (see the "Major Recommendations" field in this summary and the full version of the original guideline document for details.)

CONTRAINDICATIONS

CONTRAINDICATIONS

- All medications used in bipolar disorder are secreted in breast milk to some degree. Clozapine and lithium are generally regarded as absolute contraindications to breastfeeding due to the risk of agranulocytosis with clozapine and lithium toxicity; lithium is secreted in breast milk at 40% of the maternal serum concentration. Occasional reports of adverse neonatal effects, presumably due to transfer of the drug in the milk, have appeared. The most cautious approach is to advise that breast feeding is avoided whenever a psychotropic is prescribed but many authorities regard this as too prescriptive.
- The following drugs should not be routinely prescribed for pregnant women with bipolar disorder:
 - Valproate—because of risk to the fetus and subsequent child development
 - Carbamazepine—because of its limited efficacy and risk of harm to the fetus
 - Lithium—because risk of harm to the fetus, such as cardiac problems
 - Lamotrigine—because of the risk of harm to the fetus
 - Paroxetine—because of the risk of cardiovascular malformations in the fetus
 - Long-term treatment with benzodiazepines—because of risks during pregnancy and the immediate postnatal period, such as cleft palate and floppy baby syndrome

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Guidelines are not a substitute for professional knowledge and clinical judgement. They can be limited in their usefulness and applicability by a number of different factors: the availability of high quality research evidence, the quality of the methodology used in the development of the guideline, the generalisability of research findings and the uniqueness of individual patients.
- In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment programme including a range of activities, the purpose of which may be to help engage the patient, and provide an appropriate context for the delivery of specific interventions. It is important to maintain and enhance the service context in which these interventions are delivered,

otherwise the specific benefits of effective interventions will be lost. Indeed, the importance of organising care, so as to support and encourage a good therapeutic relationship, is at times as important as the specific treatments offered.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation in the National Health Service (NHS)

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in "Standards for better health," issues in July 2004. Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance (listed below). These are available on their website (www.nice.org.uk/CG038; see also the "Availability of Companion Documents" field, below).

- Slides highlighting key messages for local discussion
- Costing tools
 - Costing report to estimate the national savings and costs associated with implementation
 - Costing template to estimate the local costs and savings involved
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally
- Audit criteria to monitor local practice

Key Priorities for Implementation

Treating Bipolar Disorder with Drugs

- Valproate should not be prescribed routinely for women of child-bearing potential. If no effective alternative to valproate can be identified, adequate contraception should be used, and the risks of taking valproate during pregnancy should be explained.
- Lithium, olanzapine or valproate* should be considered for long-term treatment of bipolar disorder. The choice should depend on:
 - Response to previous treatments
 - The relative risk, and known precipitants, of manic versus depressive relapse
 - Physical risk factors, particularly renal disease, obesity and diabetes
 - The patient's preference and history of adherence
 - Gender (valproate should not be prescribed for women of child-bearing potential)
 - A brief assessment of cognitive state (such as the Mini-Mental State Examination) if appropriate, for example, for older people

- If the patient has frequent relapses, or symptoms continue to cause functional impairment, switching to an alternative monotherapy or adding a second prophylactic agent (lithium, olanzapine, valproate*) should be considered. Clinical state, side effects and, where relevant, blood levels should be monitored closely. Possible combinations are lithium with valproate*, lithium with olanzapine, and valproate* with olanzapine. The reasons for the choice and the discussion with the patient of the potential benefits and risks should be documented.
- If a trial of a combination of prophylactic agents proves ineffective, the following should be considered:
 - Consulting with, or referring the patient to, a clinician with expertise in the drug treatment of bipolar disorder
 - Prescribing lamotrigine* (especially if the patient has bipolar II disorder) or carbamazepine
- If a patient is taking an antidepressant at the onset of an acute manic episode, the antidepressant should be stopped. This may be done abruptly or gradually, depending on the patient's current clinical need and previous experience of discontinuation/withdrawal symptoms, and the risk of discontinuation/withdrawal symptoms of the antidepressant in question.
- After successful treatment for an acute depressive episode, patients should not routinely continue on antidepressant treatment long-term, because there is no evidence that this reduces relapse rates, and it may be associated with increased risk of switching to mania.

Monitoring Physical Health

- People with bipolar disorder should have an annual physical health review, normally in primary care, to ensure that the following are assessed each year:
 - Lipid levels, including cholesterol in all patients over 40 even if there is no other indication of risk
 - Plasma glucose levels
 - Weight
 - Smoking status and alcohol use
 - Blood pressure

Diagnosing Bipolar Disorder in Adolescents

- When diagnosing bipolar I disorder in adolescents the same criteria should be used as for adults except that:
 - Mania must be present.
 - Euphoria must be present most days, most of the time (for at least 7 days).
 - Irritability can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character; however, it should not be a core diagnostic criterion.

*Drug names are marked with an asterisk if they do not have a United Kingdom marketing authorisation for the indication in question at the time of publication. Prescribers should check each drug's summary of product characteristics (SPC) for current licensed indications.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides
Resources
Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Mental Health. Bipolar disorder: the management of bipolar disorder in adults, children, and adolescents, in primary and secondary care. Leicester (UK): British Psychological Society, Royal College of Psychiatrists; 2006. 592 p.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

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GUIDELINE DEVELOPER(S)

National Collaborating Centre for Mental Health - National Government Agency
[Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

At each guideline development meeting, all Guideline Development Group (GDG) members declared any potential conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Clinical Excellence (NICE). Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. London (UK): National Institute for Clinical Excellence (NICE); 2003 Sep. 26 p.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. NICE guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 76 p. (Clinical guideline 38). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Bipolar disorder. The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 31 p. (Clinical guideline 38). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Bipolar disorder. Slide set. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 32 p. Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Bipolar disorder. Implementation advice. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 20 p. Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. National cost-impact report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 38 p. Available from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Costing template. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. Various p. Available from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- The guidelines manual 2007. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 April. Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1076. 11 Strand, London, WC2N 5HR.

Additionally, audit criteria are available in Appendix C in the [NICE version of the guideline](#).

PATIENT RESOURCES

The following is available:

- Bipolar disorder. Understanding NICE guidance – Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 27 p.

Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N1077. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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